

REMARKS

Claims 69 and 72 have been amended. Claims 69, 70, 72, and 74 are pending and under consideration in the application.

Support for the amendment to claims 69 and 72 is found in the specification, e.g., at page 52, lines 2 to 9, and at page 3, line 30, to page 4, line 4.

35 U.S.C. § 112, first paragraph, rejection

The Examiner rejected claims 69, 70, 72, and 74 under 35 U.S.C. § 112, first paragraph, as allegedly not being enabled. See Action at page 2. Specifically, the Examiner alleged that the specification "...does not reasonably provide enablement for a method of enhancing any nucleic acid polymerase reaction comprising any nucleic acid polymerase." See *id.*

The Examiner previously rejected claims 69, 70, 72, and 74 under 35 U.S.C. § 112, first paragraph, as allegedly not being enabled in the Final Office Action mailed January 12, 2005 ("the January Final Action"). See the January Final Action, at page 3, item 5. In the January Final Action, the Examiner alleged that "...the specification, while being enabling for a method of enhancing a nucleic acid polymerase comprising (a) forming a nucleic acid polymerase reaction composition comprising (i) a nucleic acid (ii) at least one nucleic acid polymerase, wherein said polymerase is Pfu DNA polymerase and..., it does not reasonably provide enablement for a method of enhancing a nucleic acid polymerase reaction comprising: forming a nucleic acid polymerase reaction comprising: (i) a nucleic acid and any nucleic acid polymerase and...." See *id.* The Examiner then considered certain factors set forth in *In re Wands*, 858 F2d 731, (Fed.

Cir. (1988)), and made certain allegations about those factors. See *id.* at pages 3 to 7, item 5. In one such allegation, the Examiner contended that applicants' only working examples are with Pfu DNA polymerase. See *id.* at page 5, item 5.

In the Response filed on July 12, 2005, ("the July 2005 Response"), applicants asserted that the claims were enabled, and specifically pointed out that the specification included working examples with several different polymerases. See the July 2005 Response at page 3. Applicants then addressed each of the *Wands* Factors addressed by the Examiner and asserted that an analysis of those factors should result in a conclusion that the claims were enabled. See *id.* at pages 3 to 9.

In an Advisory Action mailed August 23, 2005, ("the Advisory Action"), the Examiner maintained the rejection of claims 69, 70, 72, and 74 under 35 U.S.C. § 112, first paragraph, as allegedly not being enabled. See the Advisory Action, at page 2, item 1. Specifically, the Examiner acknowledged that the specification demonstrates enhancement of nucleic acid polymerase reactions for several different polymerases other than Pfu DNA polymerase. See *id.* The Examiner then alleged that "...it is noted that the specification only demonstrates enhancement of the nucleic acid polymerases selected from the [*P*]yrococcus species and Vent DNA polymerase but does not teach or demonstrate wherein any other polymerase besides those noted above are capable of being enhanced by the claimed method and PEF composition." See *id.* The Examiner then specifically addressed the experiments discussed on page 63 of the specification and alleged that the "...specification clearly shows that the claimed method is not capable of enhancing the activity of any and all nucleic acid polymerases in the art." See *id.* Finally, the Examiner alleged that "[d]ue to the lack of guidance and

working examples in the specification, one cannot predict that a desired polymerase reaction will be enhanced using the claimed method as described.” See *id.* at page 3.

In the Response filed on February 13, 2006 (“February 2006 Response”), applicants argued that one skilled in the art could perform routine screening to determine whether a particular polymerase fell within the scope of the claim. See February 2006 Response at pages 5 to 6. Thus, even if one skilled in the art could not predict the outcome of adding PEF to a particular polymerase reaction comprising a particular polymerase, one could test whether or not PEF enhanced that particular polymerase reaction by simply running two polymerase reactions side by side. See *id.* at page 6. Applicants further noted that those experiments could be performed in a matter of hours. See *id.* Finally, applicants noted that PCR using 96-well plates was known at the time of filing, and therefore, one skilled in the art could test 48 different polymerase and PEF combinations using a single 96-well plate in a matter of hours. See *id.*

In the Action, the Examiner maintained the rejection of claims 69, 70, 72, and 74 under 35 U.S.C. § 112, first paragraph, as allegedly not being enabled. The Examiner summarized her position with regards to the Wands factors, noting specifically that “...the specification teaches that the presence of PEF may not enhance the yield of PCR products generated with Taq DNA polymerase which is isolated originally from the thermophilic eubacteria, *Thermus aquaticus*, thus suggesting that not all DNA polymerases are effective in the presence of the enhancing factor(s) claimed therein.” See Action at page 5. In response to applicants’ assertions that it would not be undue

experimentation to test a particular polymerase in a PCR reaction, the Examiner alleged that:

While the Examiner agrees that multiplex screening methodologies are readily available and known in the art, there is a significant lack of predictability in the art for the instant invention. As noted earlier, one skilled in the art cannot readily anticipate the effect of a change within the subject matter to which the claimed invention pertains. This is because it is not obvious from the disclosure of the species given in the examples, what other species will work (*be enhanced or controlled by the protein*). Therefore, the Examiner maintains that undue experimentation is necessary to practice the invention as currently claimed.

See Action at page 9. Applicants respectfully traverse.

As applicants have noted in previous responses, “[t]he test of enablement is not whether any experimentation is necessary, but whether, if experimentation is necessary, it is undue. *In re Angstadt*, 537 F.2d 498, 504, 190 U.S.P.Q. 214, 219 (CCPA 1976).” See MPEP §2164.01. Specifically, as noted in *Wands*, “[e]nablement is not precluded by the necessity for some experimentation such as routine screening.” See *Wands* at 736-37.

Applicants assert that the experimentation necessary to practice the claimed methods is not undue. As applicants noted above, even if one skilled in the art could not predict the outcome of adding PEF to a particular polymerase reaction comprising a particular polymerase, one could test whether or not PEF enhanced that particular polymerase reaction by simply running two polymerase reactions side by side. Furthermore, those experiments could be completed in a matter of hours. The Examiner does not argue against those assertions, but instead argues that undue experimentation is necessary to practice the claimed method because “there is a significant lack of predictability in the art for the instant invention.” See Action at page 9.

Applicants assert that the Examiner's conclusion ignores the evidence presented. The Examiner appears to focus on the predictability in the art, and finds that to be determinative. That determination is inconsistent with applicants' assertions about the ease of experimentation and the law that permits such experimentation. The Examiner addresses neither the ease of the experimentation nor the law that permits such experimentation.

The whole point of applicants' assertions is that even if applicants agreed that the art is unpredictable, one skilled in the art could know whether PEF enhanced a particular polymerase reaction by running a simple experiment that could be performed in a matter of hours. Thus, the Examiner's response that applicants' assertions are not convincing because the art is unpredictable is confusing. Applicants' assertion is already based on a hypothetical assumption that the art is unpredictable.

To clarify applicants' position, solely for the purposes of this hypothetical example, applicants are conceding that the art is unpredictable. Applicants assert that even in such a hypothetical situation where all of the Examiner's allegations concerning the predictability of the art are true and the relationship between PEF and particular polymerases is completely unpredictable, the amount of experimentation necessary to determine whether PEF enhanced a particular polymerase reaction would still only take a matter of hours.¹ Applicants assert that experiments that take a matter of hours do not rise to the level of undue experimentation. For comparison, the MPEP provides an

¹ Applicants do not concede this assertion concerning predictability, but merely argue here that even if the assertion were correct, the rejection fails.

example of reasonable experimentation wherein studies that cost \$50,000 and took six to twelve months failed to show undue experimentation. See MPEP § 2164.06(I).

By concluding that experiments that would take a matter of hours to complete would represent undue experimentation, the Examiner appears to be approaching a standard of enablement wherein any experimentation would represent undue experimentation. Essentially, it appears that the Examiner finds the alleged unpredictability of the art to be determinative, regardless of how easy it would be to test whether PEF enhanced a particular polymerase reaction. That is not the proper standard for enablement. As noted above, “[e]nablement is not precluded by the necessity for some experimentation such as routine screening.” See *Wands* at 736-37.

If the Examiner maintains this rejection, applicants respectfully request that she specifically address how experiments that can be performed in a matter of hours represent undue experimentation, or, in the alternative, how applicants’ assertions concerning the amount of experimentation that would be necessary are erroneous.

Applicants have previously addressed the Examiner’s allegations concerning the *Wands* factors in the July 2005 Response. Rather than repeating those comments, applicants incorporate them herein by reference. However, applicants do have the following additional comments regarding the Examiner’s characterization of the predictability of the art.

Specifically, in characterizing the art as unpredictable, the Examiner contends that, “...the specification teaches that the presence of PEF may not enhance the yield of PCR products generated with Taq DNA polymerase which is isolated originally from the thermophilic eubacteria, *Thermus aquaticus*, thus suggesting that not all DNA

polymerases are effective in the presence of the enhancing factor(s) claimed therein.”

See Action at page 5. Applicants assert that that conclusion is not suggested by the specification. The specification merely suggests that the presence of PEF “...may not enhance the yield of PCR products generated with Taq DNA polymerase.” See the specification at page 63, lines 21 to 24. There is no suggestion, however, that a DNA polymerase may not be effective in the presence of PEF, nor can that conclusion be reached from the experiment discussed on page 63 of the specification.

Additionally, applicants assert that the art is not as unpredictable as the Examiner contends. In fact, the specification provides extensive guidance on the mechanism by which PEF can enhance an amplification reaction. See the specification at page 52, line 1, to page 56, line 2. Those pages explain that dUTP can be generated in an amplification reaction by spontaneous deamination of dCTP. See the specification at page 52, lines 16 to 29. Furthermore, the specification explains that the presence of dUTP in an amplification reaction can inhibit an amplification reaction. See the specification at page 53, line 22 to page 54, line 9. Finally, the specification explains that the presence of PEF can prevent dUTP inhibition of an amplification reaction. Page 54, lines 10 to 14. Thus, one of skill in the art reading the specification would predict that PEF would have a greater or lesser effect on the amplification reaction depending on the amount of dUTP generated in the amplification reaction.

Moreover, the specification provides extensive guidance to allow one of skill in the art to make and practice the claimed invention. For example, in the specification, applicants point out that Lasken et al., *J. Biol. Chem.* 271:17,691-17,696 (1996) (“Lasken”) have shown that DNA synthesis by archaeal DNA polymerases appears to

be inhibited by dU containing DNA. A copy of Lasken is provided with this response. Furthermore, Lasken, which is incorporated by reference at page 68, lines 20 to 21 of the specification, describes methods for identifying dU sensitivity and also identifies archaeal polymerases as the polymerase class that is sensitive to dU in DNA (hence archaeal polymerases should benefit from PEF). Additionally, applicants provided guidance on how to assay for dU sensitivity in the specification. For example, Figure 21, lane 2, shows how to identify Pfu as being sensitive to dU by adding dUTP to the PCR reaction. Adding dUTP to PCR reactions is also described at pages 18, 19, 52, and 53. Also, Figure 22 shows how to identify a polymerase sensitive to dU in DNA by adding dU DNA to a polymerization assay. Furthermore, Figures 33-36 illustrate the ease of identifying which polymerases are sensitive to dUTP by simply adding PEF to a PCR reaction. Thus, applicants have shown how to identify which polymerases are enhanced by PEF, both by adding PEF to PCR reactions and by identifying polymerase sensitivity to dU in DNA.

Thus, applicants assert that the claims are enabled. Accordingly, applicants respectfully request reconsideration and withdrawal of the 35 U.S.C. §112, first paragraph, rejection of claims 69, 70, 72, and 74.


Applicants respectfully submit that the application is in condition for allowance. In the event the Examiner does not find the claims allowable, applicants request that the Examiner contact the undersigned at (650) 849-6658 to set up an interview.

If there is any fee due in connection with the filing of this Response, please
charge the fee to Deposit Account No. 06-0916.

Respectfully submitted,

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